RIVAROXABAN NEI PAZIENTI CON FIBRILLAZIONE ATRIALE E PROTESI BIOLOGICA MITRALICA

RISULTATI DEL RIVER TRIAL

BACKGROUND

- Patients with atrial fibrillation (AF) and a bioprosthetic mitral valve require long-term anticoagulation, but the optimal therapeutic strategy remains uncertain.

- The efficacy and safety of DOACs in patients with AF and a mitral bioprosthetic valve are based on subgroup analyses of pivotal trials

  ARISTOTLE (apixaban) N = 31 patients

  ENGAGE-TIMI 48 (edoxaban) N = 131 patients

  and on the findings of a pilot trial of dabigatran that enrolled 27 patients (**DAWA**)

- Patients with bioprosthetic valves were excluded from the ROCKET-AF trial.

ORIGINAL ARTICLE

Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

H.P. Guimarães, R.D. Lopes, P.G.M. de Barros e Silva, I.L. Liporace, R.O. Sampaio, F. Tarasoutchi, C.R. Hoffmann-Filho, R. de Lemos Soares Patriota, T.L.L. Leiria, D. Lamprea, D.B. Precoma, F.A. Atik, F.S. Silveira, F.R. Farias, D.O. Barreto, A.P. Almeida, A.C. Zilli, J.D. de Souza Neto, M.A. Cavalcante, F.A.M.S. Figueira, F.C.S. Kojima, L. Damiani, R.H.N. Santos, N. Valeis, V.B. Campos, J.F.K. Saraiva, F.H. Fonseca, I.M. Pinto, C.C. Magalhães, J.F.M. Ferreira, J.H. Alexander, R. Pavanello, A.B. Cavalcanti, and O. Berwanger, for the RIVER Trial Investigators*

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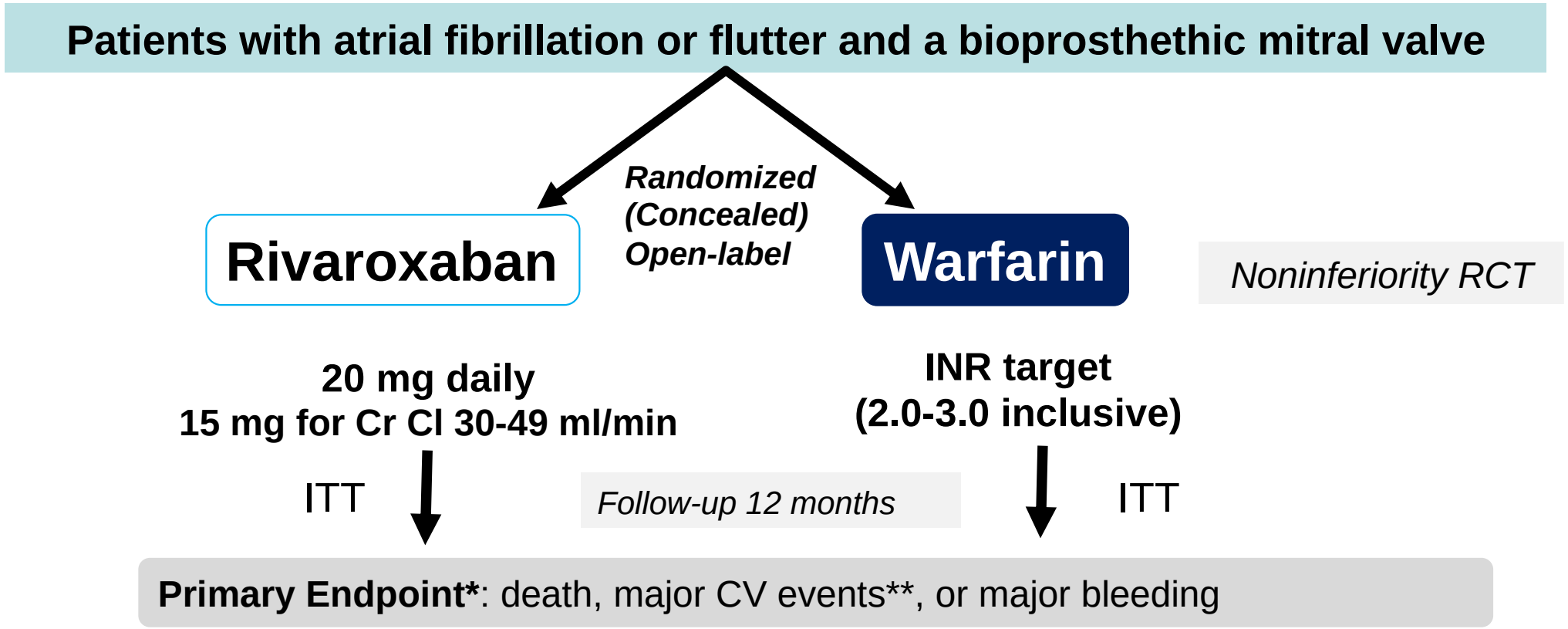
STUDY DESIGN



* adjudicated by a blinded Clinical Events Classification Committee
** stroke, TIA, valve thrombosis, systemic embolism not related to the central nervous system, or hospitalization for heart failure.

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SECONDARY ENDPOINTS

- **Efficacy**
  - Composite outcome of CV death or thromboembolic events (stroke, TIA, valve thrombosis, venous thromboembolism, or non-CNS systemic embolism)
  - Individual components of the combined endpoints

- **Safety**
  - Bleeding events (major, minor, minimal, or fatal)
  - Bleeding events are classified based on the ROCKET-AF definition, but also using the TIMI and BARC criteria

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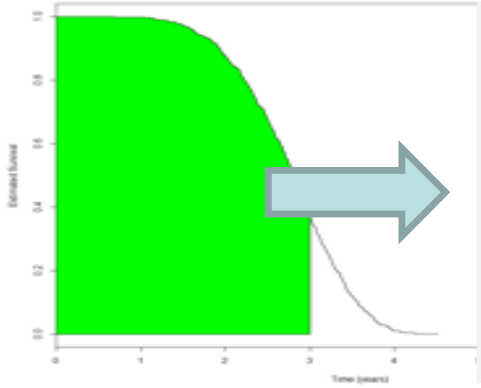
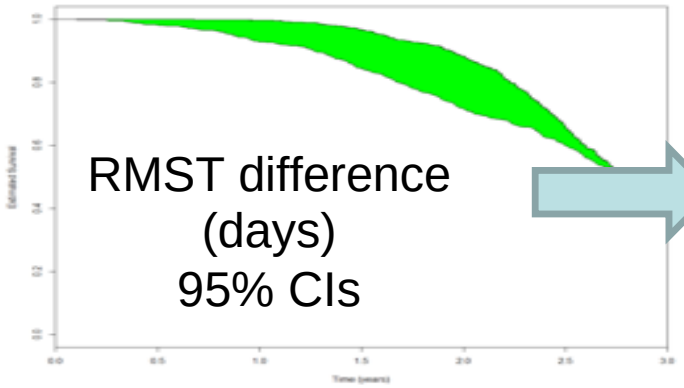
STATISTICAL ANALYSIS

- **Primary Endpoint Analysis**
  - Restricted Mean Survival Time (RMST)*:

** not dependent on the number of events and on the assumption of proportional hazards*



the mean time free from an outcome event up to 365 days, reflecting the area under the survival curve



rivaroxaban minus warfarin, so negative values indicate an increased risk from rivaroxaban treatment

- **Sample Size**
  - Noninferiority margin: between-group difference of - 8 days in the RMST (approximately 2% of 365 days). N =1000 patients
  - 80% power, event rate of 14.5% in the warfarin group, with a hazard ratio of 0.79 and an alpha level of 5%.

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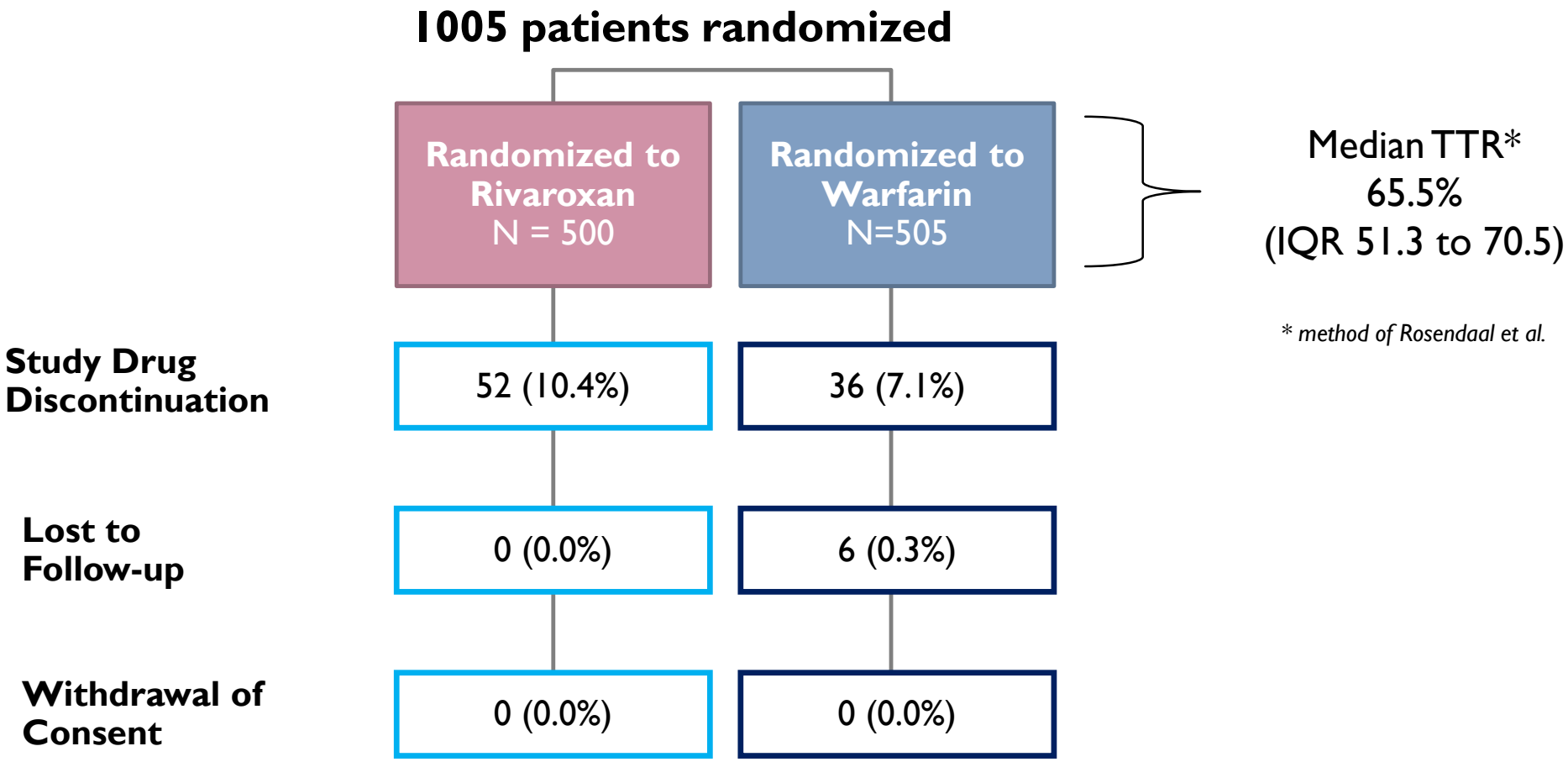
CONSORT DIAGRAM



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BASELINE CHARACTERISTICS

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Rivaroxaban (N=500)	Warfarin (N=505)	All Patients (N=1005)
Age			
Mean — yr	59.4±2.4	59.2±11.8	59.3±12.1
≥65 yr — no. (%)	179 (35.8)	176 (34.9)	355 (35.3)
Female sex — no. (%)	311 (62.2)	296 (58.6)	607 (60.4)
Medical history — no. (%)			
Diabetes mellitus	74 (14.8)	64 (12.7)	138 (13.7)
Hypertension	308 (61.6)	302 (59.8)	610 (60.7)
Dyslipidemia	176 (35.2)	162 (32.1)	338 (33.6)
Percutaneous valve intervention	39 (7.8)	37 (7.3)	76 (7.5)
Myocardial infarction	24 (4.8)	24 (4.8)	48 (4.7)
Percutaneous coronary intervention	16 (3.2)	16 (3.2)	32 (3.1)
Myocardial revascularization	27 (5.4)	19 (3.8)	46 (4.5)
Stroke	63 (12.6)	66 (13.1)	129 (12.8)
Transient ischemic attack	12 (2.4)	14 (2.8)	26 (2.5)
Peripheral vascular disease	10 (2.0)	6 (1.2)	16 (1.5)
Carotid artery disease	8 (1.6)	7 (1.4)	15 (1.4)
Congestive heart failure	202 (40.4)	188 (37.2)	390 (38.8)
Chronic kidney disease†	7 (1.4)	11 (2.2)	18 (1.7)
Current smoker — no. (%)	16 (3.2)	23 (4.6)	39 (3.8)
Median body-mass index (IQR)‡	26.6 (23.4–29.9)	25.5 (22.8–29.3)	26.0 (23.2–29.7)

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BASELINE CHARACTERISTICS

Characteristic	Rivaroxaban (N=500)	Warfarin (N=505)	All Patients (N=1005)
Race or ethnic group — no. (%)§			
White	294 (58.8)	270 (53.5)	564 (56.1)
Black	63 (12.6)	69 (13.7)	132 (13.1)
Multiracial	138 (27.6)	159 (31.5)	297 (29.5)
Asian	5 (1.0)	7 (1.4)	12 (1.1)
Type of atrial rhythm — no. (%)			
Paroxysmal fibrillation	114 (22.8)	109 (21.6)	223 (22.2)
Permanent fibrillation	311 (62.2)	310 (61.4)	621 (61.7)
Persistent fibrillation	55 (10.9)	62 (12.3)	117 (11.6)
Flutter	20 (4.0)	24 (4.8)	44 (4.3)
Median serum creatinine (IQR) — mg/dl	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.1)
Median creatinine clearance (IQR) — ml/min	77.4 (58.8–95.7)	77.7 (59.1–96.8)	77.5 (58.9–96.0)
Mean CHA_2DS_2-VASc score¶	2.7±1.5	2.5±1.3	2.6±1.4
Mean HAS-BLED score‖	1.6±0.6	1.6±0.9	1.6±0.9
Interval between mitral-valve implantation and randomization — no. (%)			
<3 mo	94 (18.8)	95(18.8)	189 (18.8)
3 mo to <1 yr	91 (18.2)	78 (15.4)	169 (16.8)
1 yr to <5 yr	160 (32.0)	164 (32.5)	324 (32.2)
5 yr to <10 yr	148 (29.6)	160 (31.7)	308 (30.6)
Missing data	7 (1.4)	8 (1.6)	15 (1.4)

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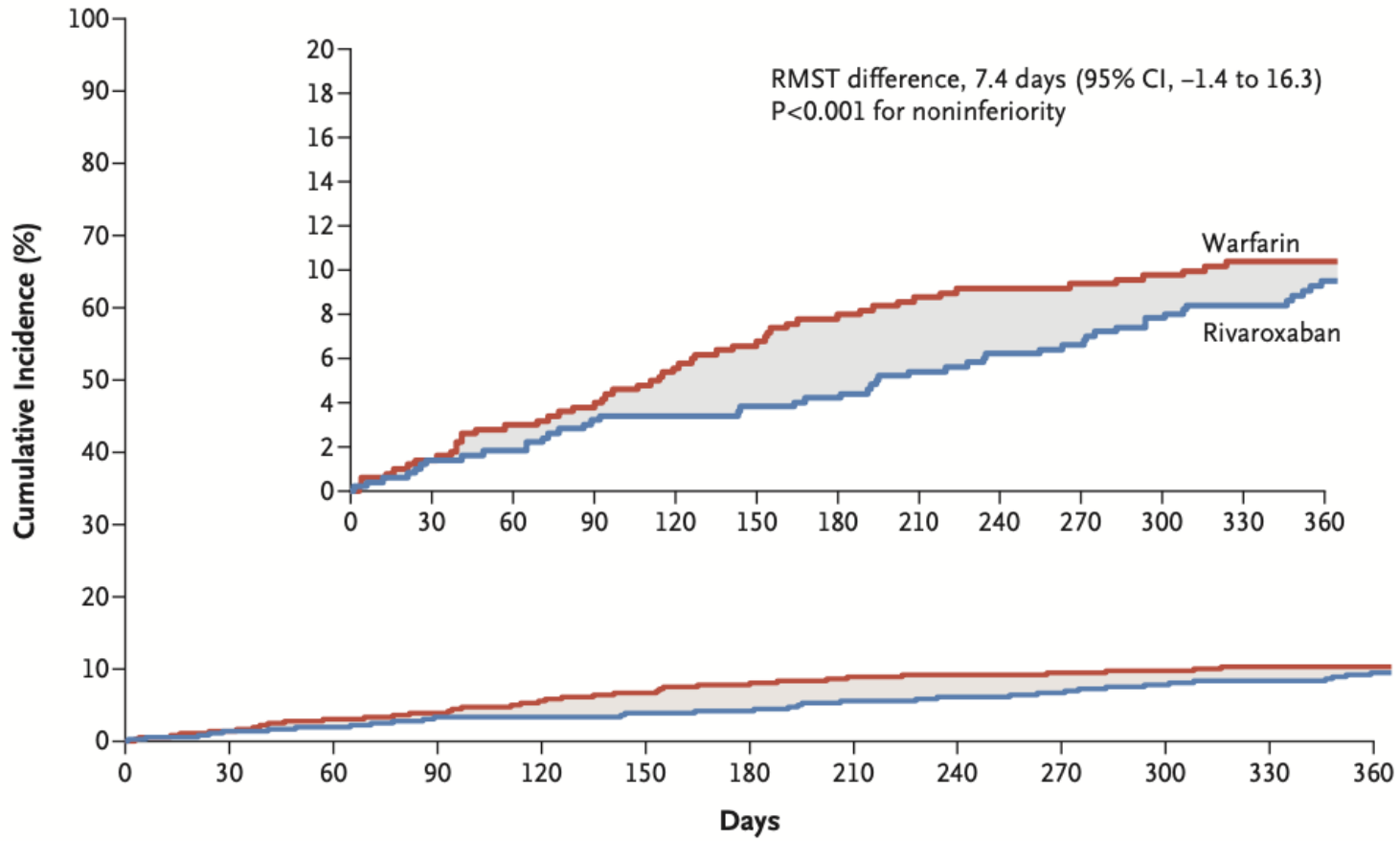
KAPLAN–MEIER ANALYSIS OF THE PRIMARY OUTCOME



No. at Risk													
Warfarin	505	496	487	483	474	469	463	458	456	455	450	445	346
Rivaroxaban	500	493	491	484	483	481	479	473	469	466	459	453	340

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SECONDARY EFFICACY OUTCOME

Secondary Outcome	Rivaroxaban (N=500)		Warfarin (N=505)		Hazard Ratio (95% CI)†
	no. (%)	*rate per 100 patient-yr*	*no. (%)*	*rate per 100 patient-yr*	
Death from cardiovascular causes or thromboembolic events — no. (%)‡	17 (3.4)	3.53	26 (5.1)	5.44	0.65 (0.35–1.20)
Stroke					
Any	3 (0.6)	0.62	12 (2.4)	2.50	0.25 (0.07–0.88)
Nonfatal	2 (0.4)	0.41	10 (2.0)	2.09	0.20 (0.04–0.91)
Fatal	1 (0.2)	0.20	2 (0.4)	0.39	0.50 (0.05–5.50)
Hemorrhagic	0	0	5 (1.0)	1.03	NA
Ischemic	3 (0.6)	0.62	7 (1.4)	1.45	0.43 (0.11–1.66)
Transient ischemic attack	0	0	1 (0.2)	0.21	NA
Death					
Any	20 (4.0)	4.12	20 (4.0)	4.11	1.01 (0.54–1.87)
From cardiovascular causes	11 (2.2)	2.27	13 (2.6)	2.67	0.85 (0.38–1.90)
Valve thrombosis	5 (1.0)	1.04	3 (0.6)	0.62	1.68 (0.40–7.01)
Non-CNS systemic embolism	0	0	1 (0.2)	0.21	NA
Hospitalization for heart failure	22 (4.4)	4.43	19 (3.8)	3.78	1.15 (0.62–2.13)

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SAFETY OUTCOME

Bleeding Event	Rivaroxaban (N=500)		Warfarin (N=505)		Hazard Ratio (95% CI)†
	no. (%)	*rate per 100 patient-yr*	*no. (%)*	*rate per 100 patient-yr*	
Any bleeding	65 (13.0)	14.71	78 (15.4)	17.99	0.83 (0.59–1.15)
Major bleeding	7 (1.4)	1.46	13 (2.6)	2.72	0.54 (0.21–1.35)
Intracranial bleeding	0	0	5 (1.0)	1.03	NA
Fatal bleeding	0	0	2 (0.4)	0.41	NA
Clinically relevant nonmajor bleeding	24 (4.8)	5.12	23 (4.6)	4.87	1.05 (0.60–1.87)
Minor bleeding	37 (7.4)	8.03	49 (9.7)	10.84	0.75 (0.49–1.15)

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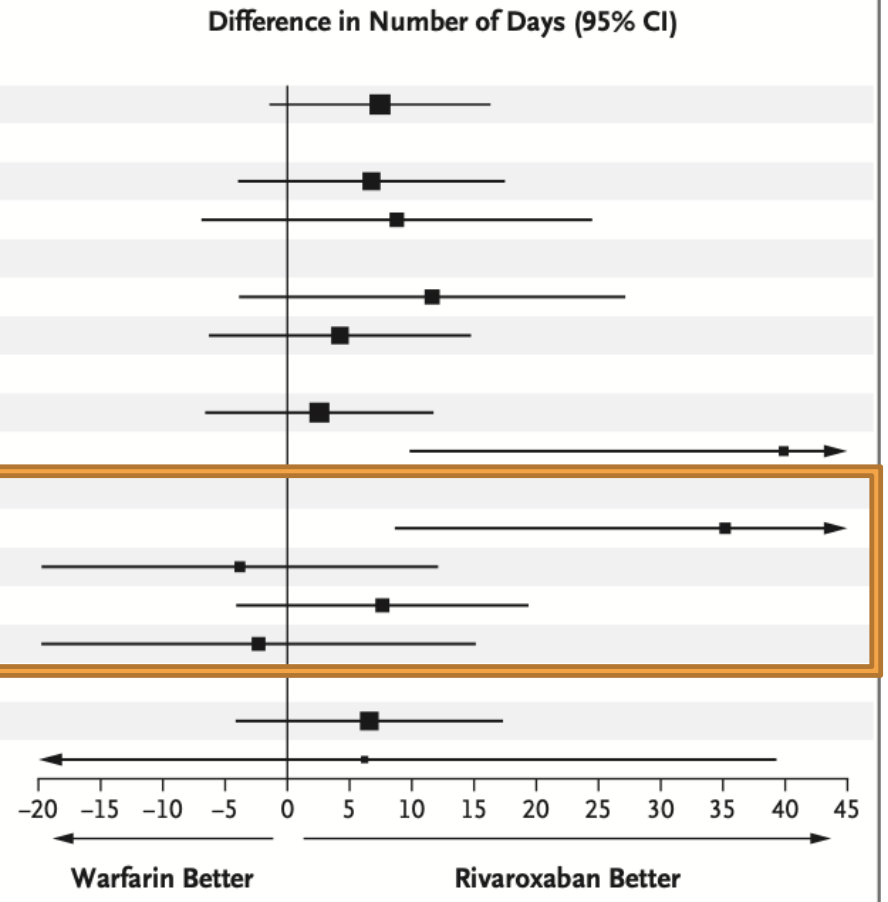
SUBGROUP ANALYSIS OF THE PRIMARY OUTCOME

Subgroup	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin
	no. of events/total no. (%)		*no. of days until outcome (95% CI)*	
All patients	47/500 (9.4)	52/505 (10.3)	347.5 (341.8–353.1)	340.1 (333.2–346.9)
Age				
<65 yr	28/321 (8.7)	30/329 (9.1)	349.0 (342.1–355.8)	342.2 (334.0–350.5)
≥65 yr	19/179 (10.6)	22/176 (12.5)	344.8 (335.0–354.7)	336.0 (323.8–348.3)
Sex				
Male	20/189 (10.6)	25/209 (12.0)	345.2 (335.4–355.0)	333.6 (321.6–345.6)
Female	27/311 (8.7)	27/296 (9.1)	348.9 (342.0–355.7)	344.6 (336.6–352.6)
Antiplatelet therapy at baseline				
No	41/425 (9.6)	39/441 (8.8)	346.7 (340.4–353.0)	344.1 (337.4–350.8)
Yes	6/75 (8.0)	13/64 (20.3)	352.2 (340.3–364.0)	312.3 (284.6–339.9)
Time since mitral-valve implantation				
<3 mo	6/94 (6.4)	18/95 (18.9)	348.6 (335.1–362.1)	313.5 (290.6–336.3)
3 mo to <1 yr	6/91 (6.6)	4/78 (5.1)	351.3 (339.3–363.3)	355.1 (344.6–365.6)
1 yr to <5 yr	7/160 (4.4)	14/164 (8.5)	356.2 (348.8–363.6)	348.6 (339.4–357.7)
≥5 yr	27/148 (18.2)	16/160 (10.0)	336.3 (324.1–348.5)	338.6 (326.2–351.1)
Creatinine clearance (ml/min)				
≥50	33/361 (9.1)	36/358 (10.1)	346.8 (339.9–353.7)	340.2 (332.0–348.5)
<50	6/47 (12.8)	10/60 (16.7)	334.8 (310.6–359.0)	328.6 (306.0–351.2)



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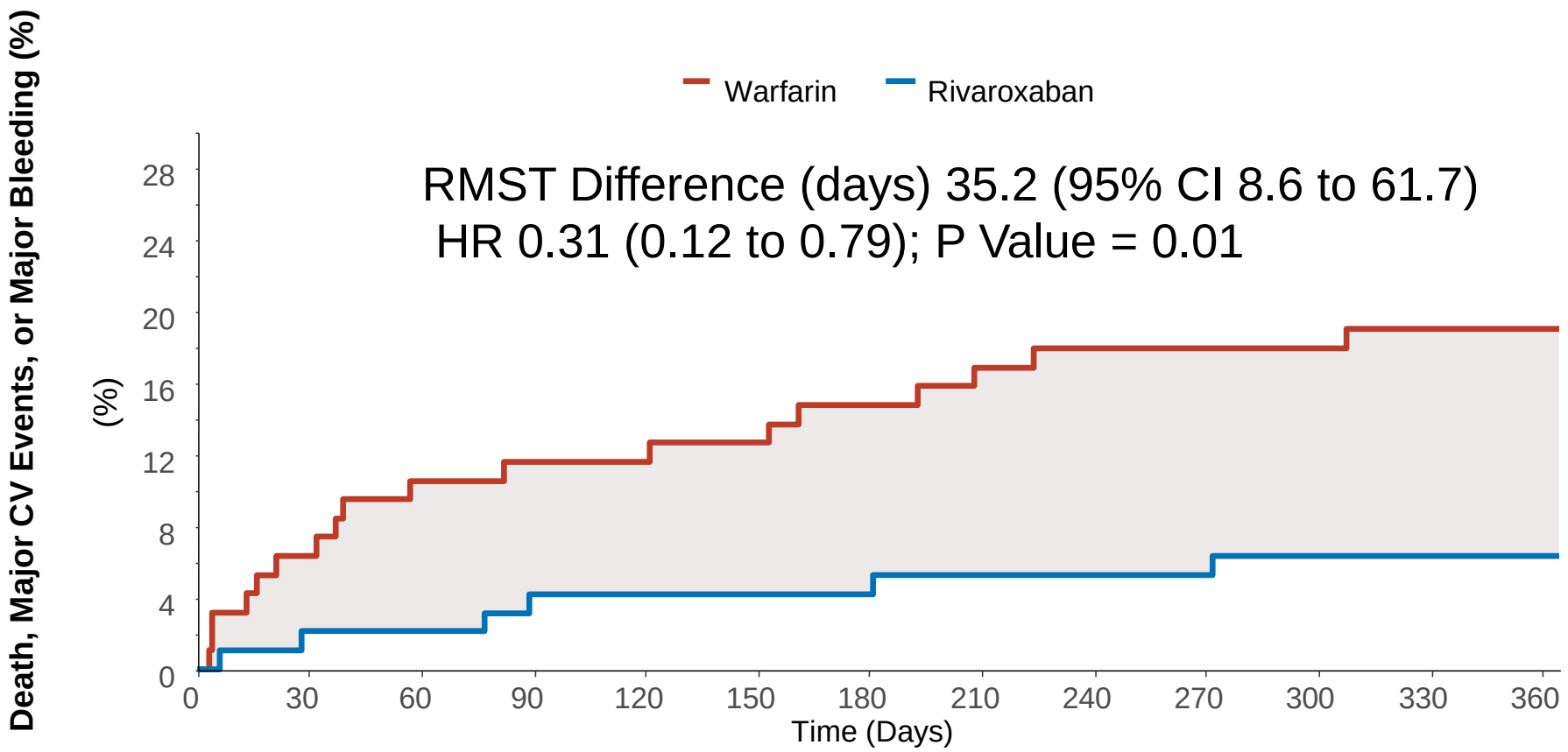
TIME FROM MITRAL VALVE IMPLANTATION < 3 MONTHS



Patients at risk

Rivaroxaban	94	92	92	90	90	90	90	89	89	88	87	87	69
Warfarin	95	89	85	84	84	83	81	79	78	78	76	74	64

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LIMITATIONS

- The open-label design could have introduced bias in the ascertainment or reporting of events.
  - blinded end-point adjudication process and regular training and monitoring of personnel at the trial sites.

- Findings cannot be extrapolated to patients with a bioprosthetic aortic valve or to those with mitral stenosis or mechanical valves.
  - Ongoing PROACT Xa (apixaban versus warfarin in patients with a mechanical On-X aortic heart valve)
  - Ongoing INVICTUS rheumatic heart disease research program: rivaroxaban compared to VKA in rheumatic valvular disease and AF.

- The as-treated and per-protocol analyses used restricted populations based on post-randomization variables such as adherence to the trial drugs, which could have influenced these results.

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CONCLUSIONS

- In conclusion, in patients with atrial fibrillation and a bioprosthetic mitral valve, rivaroxaban is noninferior to warfarin with respect to mean time free from death, major cardiovascular events, or major bleeding.

- Since rivaroxaban does not require monitoring and has a more consistent anticoagulant effect, which is less influenced by food or concomitant medications, it represents an attractive alternative to warfarin for this patient population

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